

Reduced exposure to vasopressors through permissive hypotension to reduce mortality in critically ill people aged 65 and over: the 65 RCT

Paul R Mouncey,^{1*} Alvin Richards-Belle,¹
Karen Thomas,¹ David A Harrison,¹ M Zia Sadique,²
Richard D Grieve,² Julie Camsooksai,³
Robert Darnell,¹ Anthony C Gordon,^{4,5}
Doreen Henry,⁶ Nicholas Hudson,¹ Alexina J Mason,⁴
Michelle Saull,¹ Chris Whitman,⁶ J Duncan Young,⁷
François Lamontagne,^{8,9} Kathryn M Rowan¹
and the 65 trial investigators†

¹Clinical Trials Unit, Intensive Care National Audit & Research Centre, London, UK

²Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, London, UK

³Critical Care, Research and Innovation, Poole Hospital NHS Foundation Trust, Poole, UK

⁴Division of Anaesthetics, Pain Medicine and Intensive Care, Imperial College London, London, UK

⁵Intensive Care Unit, Imperial College Healthcare NHS Trust, St Mary's Hospital, London, UK

⁶Patient representative, UK

⁷Kadoorie Centre for Critical Care Research and Education, University of Oxford, John Radcliffe Hospital, Oxford, UK

⁸Department of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada

⁹Centre de Recherche du Centre Hospitalier, Université de Sherbrooke, Sherbrooke, QC, Canada

*Corresponding author Paul.Mouncey@icnarc.org

†The 65 trial investigators are listed in *Appendix 1*.

Declared competing interests of authors: Richard D Grieve is a member of the National Institute for Health Research Health Technology Assessment Commissioning Board (2018–present). Anthony C Gordon has received a grant for a National Institute for Health Research Research Professorship; personal fees and non-financial support from Orion Corporation (Espoo, Finland) and Orion Pharma (Newbury, UK); a grant and consulting fees paid to his institution from Tenax Therapeutics (Morrisville, NC, USA); consulting fees paid to his institution from Bristol Myers Squibb (New York, NY, USA); and consulting fees paid to his institution from GlaxoSmithKline plc (Brentford, UK). J Duncan Young was a Consultant Advisor to the National Institute for Health Research/Medical Research Council Efficacy and Mechanism Evaluation programme, a member of the Efficacy and Mechanism Evaluation Strategy Advisory Committee, the Efficacy and Mechanism Evaluation Funding Committee, and the Efficacy and Mechanism Evaluation Funding Committee Sub-Group Remit and Competitiveness Check group, from February 2011 to December 2018. Kathryn M Rowan was a member of the National Institute for Health Research Health Services and Delivery Research Board (2014–19).

Published February 2021

DOI: 10.3310/hta25140

Scientific summary

The 65 RCT

Health Technology Assessment 2021; Vol. 25: No. 14

DOI: 10.3310/hta25140

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Vasopressors are life-sustaining drugs that are administered to patients in critical care to avoid hypotension, which is associated with myocardial injury, kidney injury and death. However, they work by causing vasoconstriction, which may reduce blood flow and cause other secondary effects on cardiac, metabolic, microbiome and immune function.

To guide vasopressor administration, doctors typically prescribe a mean arterial pressure target and bedside nurses adjust the dose/rate of vasopressor infusions to achieve the target mean arterial pressure. The 2012 Surviving Sepsis Campaign guidelines recommended maintaining a mean arterial pressure of > 65 mmHg (Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;**39**:165–228); however, the guidelines were based on low-quality evidence and did not provide guidance for an upper limit. The guidelines also suggested a higher mean arterial pressure target for older patients and those with chronic hypertension, recommendations that were later removed in 2016. Studies suggest that, as the optimal mean arterial pressure target is not well established, clinicians tend to err on the side of targeting higher mean arterial pressures, potentially exposing patients to greater doses and durations of vasopressors than may be necessary.

An individual patient data meta-analysis of two randomised clinical trials that evaluated different mean arterial pressure targets suggested that increased exposure to vasopressors, through targeting higher mean arterial pressures, may be associated with a greater risk of death in older critically ill patients (Lamontagne F, Day AG, Meade MO, Cook DJ, Guyatt GH, Hylands M, *et al.* Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. *Intensive Care Med* 2018;**44**:12–21; Lamontagne F, Meade MO, Hébert PC, Asfar P, Lauzier F, Seely AJE, *et al.* Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. *Intensive Care Med* 2016;**42**:542–50; and Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, *et al.* High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014;**370**:1583–93).

Aim and objective

Aim

The aim was to estimate the clinical effectiveness and cost-effectiveness of reduced vasopressor exposure through permissive hypotension (i.e. a lower mean arterial pressure target of 60–65 mmHg) in older critically ill patients.

Objective

The objective was to estimate the clinical effectiveness and cost-effectiveness of permissive hypotension when compared with usual care.

Methods

Trial design and governance

The 65 trial was a pragmatic, multicentre, parallel-group, open-label, randomised clinical trial of reduced exposure to vasopressors through permissive hypotension (i.e. a lower mean arterial pressure

target of 60–65 mmHg), with an integrated economic evaluation. The trial was nested in the Case Mix Programme (i.e. the national clinical audit for adult critical care). The Health Research Authority (London, UK) and the South Central – Oxford C Research Ethics Committee (Oxford, UK) approved the trial. The National Institute for Health Research convened a majority independent Trial Steering Committee and an independent Data Monitoring and Ethics Committee. The trial was sponsored by the Intensive Care National Audit & Research Centre (London, UK) and co-ordinated by the Intensive Care National Audit & Research Centre Clinical Trials Unit.

Participants: sites and patients

Based on Case Mix Programme data, a sample size of 2600 patients (i.e. 1300 patients per group) was calculated to provide 90% power to detect as statistically significant ($p < 0.05$) a 6% absolute risk reduction.

Across 65 NHS adult general critical care units ('sites'), patients were screened and randomised if:

- they were aged ≥ 65 years
- they had vasodilatory hypotension (assessed by treating clinician)
- they had started an infusion (for at least 1 hour) of vasopressors within the prior 6 hours (if noradrenaline, then a minimum infusion rate of 0.1 $\mu\text{g}/\text{kg}/\text{minute}$ was required)
- they had adequate fluid resuscitation completed or ongoing
- vasopressors were expected to be continued for ≥ 6 further hours.

Owing to the emergency and time-sensitive nature of critical care and vasopressor administration, the Research Ethics Committee granted an emergency waiver of consent and a research without prior consent model was used (i.e. consent was sought after randomisation). Patients were randomised (by telephone or internet) in a 1 : 1 ratio, using permuted blocks of variable length and stratified by site to either the permissive hypotension (intervention) group or the usual-care (control) group.

Treatment groups

'Permissive hypotension' aimed to reduce exposure (i.e. dose and duration) to vasopressors through use of a lower mean arterial pressure target range (60–65 mmHg) to guide vasopressor administration. The choice of vasopressor was at the discretion of the treating clinician, with administration (aside from the mean arterial pressure target) as per local practice and guidelines. The decision to discontinue vasopressors depended on the patient's ability to maintain the mean arterial pressure targeted by the protocol without vasopressors. Clinical teams were actively reminded to consider discontinuing vasopressors if patients were able to maintain mean arterial pressure values of at least 60 mmHg.

Patients randomised to the usual-care group received usual vasopressor exposure (including the mean arterial pressure target) at the discretion of the treating clinician and as per local practice and guidelines.

Treating clinician(s) were aware of treatment allocations. All other usual care was provided at the discretion of the treating clinical team, as per local practice.

Outcome measures

The primary clinical outcome was all-cause mortality at 90 days. The primary cost-effectiveness outcome was incremental net monetary benefit at 90 days.

Secondary outcomes were mortality at discharge from critical care and acute hospital; duration of survival to longest available follow-up; receipt and duration of advanced respiratory and renal support during the critical care stay; days alive and free of advanced respiratory support and renal support to 28 days; duration of critical care and acute hospital stay; and questionnaire assessment of cognitive decline (using the Informant Questionnaire on Cognitive Decline in the Elderly short version) and

health-related quality of life (using the EuroQol-5 Dimensions, five-level version) at 90 days and 1 year. Secondary economic outcomes included resource use, costs and incremental net monetary benefit at 1 year. Adverse events were monitored to critical care unit discharge.

Data sources

A secure, dedicated electronic case report form enabled trial data to be entered by local site research teams. To maximise efficiency, trial data were linked to the Case Mix Programme (via the Intensive Care National Audit & Research Centre) and national death registrations (via NHS Digital) for patient characteristic, treatment and outcome data. Surviving patients were mailed questionnaires at 90 days and 1 year, with telephone follow-up to non-responders.

Analysis principles

Analyses followed the intention-to-treat principle and tested for superiority, following a prespecified published statistical analysis plan. A p -value of 0.05 was considered statistically significant. All tests were two-sided, with no adjustment for multiple comparisons. Effect estimates were reported with 95% confidence intervals. Continuous variables were reported as means and standard deviations or medians and interquartile ranges. Categorical variables were reported as counts and proportions. Missing data were handled by multiple imputation.

Analysis methods

Fisher's exact test compared between-group differences in the primary clinical outcome. The absolute risk reduction was reported with 95% confidence intervals and without adjustment as the primary effect estimate. Secondary and sensitivity analyses of the primary outcome were conducted, including an analysis adjusted for baseline data using multilevel logistic regression with a random effect of site. We also carried out prespecified subgroup analyses of the primary outcome testing interactions for age, chronic hypertension, chronic heart failure, atherosclerotic disease, Intensive Care National Audit & Research Centre risk of death score, Sepsis-3 category and vasopressors received at randomisation. Likelihood ratio tests were used to compare models with and without the relevant interaction terms.

The cost-effectiveness analyses took an NHS and Personal Social Services perspective, as recommended by the National Institute for Health and Care Excellence (London, UK), and reported quality-adjusted life-years by combining survival data with EuroQol-5 Dimensions, five-level version, index scores that used the valuation set for England. We estimated the corresponding incremental net monetary benefit by valuing incremental quality-adjusted life-years at the National Institute for Health and Care Excellence recommended threshold (£20,000) for a quality-adjusted life-year gain and subtracting incremental costs. The main assumptions were subjected to extensive sensitivity analyses.

Results

Sites and patients

Across the 65 sites, 2930 potentially eligible patients were identified, of whom 2600 were randomised between 3 July 2017 and 16 March 2019. Randomisation occurred 24 hours per day and 7 days per week. Two patients were randomised twice, resulting in 2598 unique patients (permissive hypotension, $n = 1291$; usual care, $n = 1307$). After accounting for refusals and withdrawals of consent, 2463 patients were analysed for the primary outcome (permissive hypotension, $n = 1221$; usual care, $n = 1242$). The randomised groups were well matched at baseline. In both groups, the mean age of patients was 75 years and just under half (46%) had chronic hypertension. Prior to randomisation, the mean arterial pressure was 69.9 mmHg in the permissive hypotension group and 71.1 mmHg in the usual-care group.

Clinical management

Vasopressor management diverged immediately post randomisation. During the first episode of vasopressors, permissive hypotension resulted in a lower exposure to vasopressors than did usual care, in terms of both mean duration (46.0 vs. 55.9 hours, mean difference -9.9 hours, 95% confidence interval -14.3 to -5.5 hours) and mean total noradrenaline-equivalent dose (31.5 mg vs. 44.3 mg, mean difference -12.8 mg, 95% confidence interval -18.0 mg to -7.6 mg).

Mean and peak mean arterial pressure values were lower in the permissive hypotension group. One or more occurrence of non-adherence occurred in 153 (11.9%) patients and, overall, non-adherence represented 6% of the total time receiving vasopressors in the permissive hypotension group.

Clinical effectiveness

Primary outcome

At 90 days, 500 (41.0%) patients in the permissive hypotension group and 544 (43.8%) patients in the usual-care group had died (absolute risk difference -2.85% , 95% confidence interval -6.75% to 1.05% ; $p = 0.154$). When adjusted for prespecified baseline variables, the odds ratio for 90-day mortality was 0.82 (95% confidence interval 0.68 to 0.98), compared with an unadjusted odds ratio of 0.89 (95% confidence interval 0.76 to 1.04). Secondary and sensitivity analyses did not significantly alter the primary result.

There was no evidence of heterogeneity of treatment effect according to prespecified subgroups; however, differences by chronic hypertension status were observed. For patients with chronic hypertension, 90-day mortality was 38.2% in the permissive hypotension group and 44.3% in the usual-care group (adjusted odds ratio 0.67, 95% confidence interval 0.51 to 0.88), compared with 43.3% and 43.4%, respectively, in patients without chronic hypertension (adjusted odds ratio 0.97, 95% confidence interval 0.76 to 1.24) (test of interaction $p = 0.047$, not adjusted for multiple testing).

Secondary outcomes

At acute hospital discharge, 484 (39.3%) patients in the permissive hypotension group and 519 (41.5%) patients in the usual-care group had died (absolute risk difference -2.23% , 95% confidence interval -6.09% to 1.63%). Mean days alive and free of renal support to day 28 was 17.4 (standard deviation 13.2) days and 16.7 (standard deviation 13.4) days for permissive hypotension and usual care, respectively. Other secondary outcomes, including critical care unit and acute hospital length of stay, were similar between the groups. Cognitive decline, assessed in survivors at 90 days and 1 year using the Informant Questionnaire on Cognitive Decline in the Elderly, was also similar.

Cost-effectiveness

At 90 days, the average cost and mean EuroQol-5 Dimensions, five-level version, index scores were similar between groups. After adjustment for baseline characteristics, the incremental life-years and quality-adjusted life-years were higher in the permissive hypotension group, with the majority of points (95%) in the quadrants on the cost-effectiveness plane where permissive hypotension had higher mean quality-adjusted life-years. Hence, the incremental net monetary benefit for permissive hypotension compared with usual care was positive, but with a wide confidence interval. At £20,000 per quality-adjusted life-year, the incremental net monetary benefit was £378 (95% confidence interval $-\text{£}1347$ to $\text{£}2103$). The probability that permissive hypotension is cost-effective is 70% at the £20,000 per quality-adjusted life-year threshold.

Conclusions

In patients aged ≥ 65 years who received vasopressors for vasodilatory hypotension, permissive hypotension did not significantly reduce mortality at 90 days. The absolute treatment effect on 90-day mortality, based on the 95% confidence intervals, was between a 6.8-percentage reduction and a 1.1-percentage increase in mortality at 90 days.

Implications for health care

Our results suggest that reducing exposure to vasopressors through permissive hypotension is unlikely to be harmful and may even be beneficial for older critically ill patients, in keeping with recent trends in reducing the intensity of other critical care interventions and associated side effects.

Recommendations for research

Recommendation 1

The opportunity to pool our data with those of the two previous randomised clinical trials (Lamontagne F, Meade MO, Hébert PC, Asfar P, Lauzier F, Seely AJE, *et al.* Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. *Intensive Care Med* 2016;**42**:542–50; and Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, *et al.* High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014;**370**:1583–93) will give additional power for evaluating this group of patients, including other potentially important subgroups. As this will include data from the UK, France and Canada, it will enhance generalisability and improve knowledge on this important area for critical care worldwide.

Recommendation 2

Further research should study the efficient conduct of our trial, which used simple, straightforward procedures and a research without prior consent model, to further understand the implications of these procedures with the hope of producing guidance for future studies in the critical care setting.

Trial registration

This trial is registered as ISRCTN10580502.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 14. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HS&DR programme or one of its preceding programmes as project number 15/80/39. The contractual start date was in March 2017. The final report began editorial review in February 2020 and was accepted for publication in November 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HS&DR editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HS&DR programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HS&DR programme or the Department of Health and Social Care.

© Queen's Printer and Controller of HMSO 2021. This work was produced by Mouncey *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

NIHR Journals Library Editor-in-Chief

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

NIHR Journals Library Editors

Professor John Powell Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Professor of Digital Health Care, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor Andrée Le May Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, PGfAR, PHR journals

Professor Matthias Beck Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont Senior Scientific Adviser (Evidence Use), Wessex Institute, University of Southampton, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Emeritus Professor of Wellbeing Research, University of Winchester, UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk